

²⁵²Cf neutron brachytherapy and external ⁶⁰Co photon therapy in the curative management of primary or recurrent rectal cancer

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The aim of this study was to improve the survival and local control of patients with primary or recurrent rectal cancer treated by combined external photon and intracavitary neutron radiation therapy. Analysis of this group of patients was undertaken to assess the survival, local control and complication rate in comparison with external photon therapy alone.

Materials and methods. Fifty-six patients (Co–Cf group) with rectal malignancies (T2–7 pts, T3–33 pts, T4–7 pts, 1 with melanoma and 8 with rectal carcinoma recurrence) were treated by combined radiation therapy: external ⁶⁰Co gamma irradiation (2 Gy per fraction, 3–5 fractions/week, mean total dose 37.2 Gy) and ²⁵²Cf neutron high dose rate (HDR) remote afterloading brachytherapy (0.7–2.1 Gy per fraction, 2 fractions/week, mean total dose 5.4 Gy). This group was compared with historical Co group of 52 patients (T1 – 1 pt, T2 – 12 pts, T3 – 39 pts, T4 – 2 pts; 8 with rectal carcinoma recurrence) treated by external photon radiation therapy (2 Gy per fraction, 5 fractions/week, mean total dose 62.6 Gy). The follow-up for these patients ranged from 7.5 to 12.5 years.

Results. Complete response was achieved in 19.2% and partial response in 59.6% of the cases among Co–Cf group patients. The mean total brachytherapy dose for patients with NR was less than 4.0 Gy. Acute reactions (Grade 2–4 RTOG) and late complications (Grade 2–4 RTOG) in the rectum and adjacent tissues after a 4 year follow-up were observed in 21.4% (12/56) *versus* 30.0% and 16.0% (8/50) *versus* 29.0% cases in the Co–Cf and Co groups, respectively.

The one-, two-, three-, four-, five- and six-year survival was 80.4%, 53.6%, 42.7%, 25.6%, 17.7%, 11.8% *versus* 71.6%, 41.8%, 20.9%, 10.5%, 3.0%, 1.5% for the Co–Cf and Co groups of patients respectively (a statistically significant difference of survival from one to six years).

Conclusions. The results achieved by the use of ²⁵²Cf neutron brachytherapy are encouraging to improve the treatment results in selected groups of patients with locally spread primary or recurrent rectal cancer.

Key words: rectal cancer, neutron therapy, external photon therapy, californium-252

INTRODUCTION

Several attempts were made in last decades to improve the local effectiveness of radiation therapy of rectal carcinoma by the use of intracavitary and interstitial gamma or X-ray brachytherapy (1, 2), high dose rate intraoperative radiation therapy (3) and high-LET irradiation particularly by external beams of fast neutrons (4). The basic idea was that the dose was confined to the tumour around the sources in applicators or delivered from the X-ray machine, thus avoiding a

large dose to the normal radiosensitive pelvic tissues (5, 6). The suggestion that high-LET neutron radiation could provide an additional effect was supported by the experimental data showing that the sensitivity of cancer cells to neutron radiation little depended on the oxygen level and cell status (7).

About 60% of the rectal cancer patients diagnosed every year in Lithuania have a locally spread disease (Table 1). The most favorable results are reported for patients who are able to undergo surgery as a component of combined therapy.

Table 1. Rectum carcinoma in Lithuania by stage in 1992–2002
Total – 419 pts

Stage	I + II		III		IV		Without staging	
	1992	2002	1992	2002	1992	2002	1992	2002
Male	34.7%	30.9%	40.8%	32.4%	14.0%	27.7%	10.0%	9.0%
Female	33.3%	29.9%	35.7%	35.7%	17.3%	24.8%	13.7%	9.6%
All patients	34.1%	30.5%	38.4%	33.9%	15.5%	26.3%	12.0%	9.3%

Table 2. Patient and treatment characteristics

	Co–Cf group	Co group
Number of patients	56	52
Age, years (mean)	70.4	69.7
(range)	51–89	31–83
Male/female	35/21	32/20
Diagnosis		
Ca recti	45 (80.3%)	40 (76.9%)
Ca ani	3 (5.4%)	4 (7.7%)
Recurrence	8 (14.3%)	8 (15.4%)
External 60 Co irradiation		
Total dose (Gy) (mean)	37.2	62.6
(range)	30–60	46–76
Technique		
2 fields	49	31 (plus rotation after 40 Gy)
3 fields	3	21
4 fields	4	0
Dose per fraction (Gy) (mean)	2.0	2.0
Intracavitary ²⁵² Cf neutron radiation therapy		
Dose per fraction, Gy (mean, range)	0.9 (0.7–2.1)	
Total dose, Gy (mean, range)	5.4 (2.1–8.9)	
Fractions per week (mean, range)	1.9 (1–4)	
Total number of fractions (mean, range)	5.8 (1–11)	

Table 3. Rectal tumour characteristics

	Co–Cf group	Co group
TNM		
T1:T2:T3:T4	1:7:33:7	1:12:29:2
M0:M1	48:0	44:0
Recurrence	8 (14.3%)	8 (15.4%)
Intraluminal location		
anus (2 cm)	3 (5.4%)	4 (7.7%)
inferior (2–7 cm)	26 (46.4%)	29 (55.8%)
medialis (7–11 cm)	24 (42.9%)	17 (32.7%)
superior (11–15 cm)	3 (5.3%)	2 (3.8%)
Histology		
adenoCa	49 (87.5%)	48 (92.3%)
melanoma	1 (1.8%)	–
Ca planocell	6 (10.7%)	4 (7.7%)
Growth mode		
egzophytic	11 (19.6%)	11 (21.1%)
endophytic	24 (42.9%)	16 (30.8%)
mixed	21 (37.5%)	25 (48.1%)
Tumour size		
length (cm) (mean, range)	3.87 (2–8)	3.96 (2–8)

However, there is a subset of patients who are unable to undergo surgery for different reasons. In Lithuania, in the nineties of the last century, the majority of these patients received external photon therapy with or without chemotherapy. Unfortunately, the curative photon radiation therapy has a limited benefit, because rectal adenocarcinoma is radioresistant (8), while the adjacent tissues and organs are relatively radiosensitive.

Since late 1988, combined radiation therapy (external ⁶⁰Co photon radiation plus intracavitary ²⁵²Cf neutron brachytherapy) was applied for rectal carcinoma patients unable to undergo surgery at the Lithuanian Oncology Center, seeking to prolong their survival in comparison with external photon radiation therapy.

MATERIALS AND METHODS

One hundred and eight patients with primary or recurrent rectum carcinoma were treated with

curative intent by radiation therapy: 56 patients of the Co-Cf group (1988–1993) received external ^{60}Co gamma radiation and ^{252}Cf neutron brachytherapy and 52 patients from the Co group (1985–1990) were treated by external ^{60}Co gamma radiation therapy. Patient, treatment and tumour characteristics are presented in Tables 2 and 3, respectively.

Fifty-three patients from the Co-Cf group received external gamma irradiation during this session, three patients with recurrences had received radiotherapy (58 Gy, 40 Gy, 60 Gy) more than 2 years ago and were irradiated only with ^{252}Cf brachytherapy. In most cases external gamma therapy alone (two-field technique – PA and AP 12–13 × 16–17 cm) was completed after 25–30 Gy and continued until 40 Gy with ^{252}Cf brachytherapy added.

^{252}Cf brachytherapy was performed by neutron remote after ANET-V (Russia) loaded with a ^{252}Cf source (active length 1 cm). The californium-252 content was 0.5 mg each in two lateral channels and 1.7 mg in the central channel. The irradiation procedure is based on sending the ^{252}Cf source remotely controlled into the central applicator inserted in the rectum, moving step by step from one position to another according to a calculated programme, after which the source automatically returns to the storage at the end of the irradiation programme. The dose point (100% isodose) was 1.5 cm from the central axis of the ^{252}Cf source movement trajectory (or at a depth of 5 mm from the surface of rectum mucosa), and the 50% isodose was observed at a distance of 2.5 cm from the central axis. As a rule, the length of the intracavitary volume was extended 2 cm to both sides of the gross tumour.

Topometrical investigations were performed by the use of AP and lateral radiographs or xeroentgenograms with a rectostat and dummy sources inserted into the rectum. A special computer programme was employed for the dosimetric and radiobiological planning procedure according to the principles presented elsewhere (9), (10).

The Co group was treated by a two-three-field technique (one PA) plus rotation in the prone position (angle 240°). Three patients with anal carcinoma were irradiated by two AP-PA fields and a perineum field.

Consequently, in most cases the external and internal iliac lymphnodes, presacral tissues received a

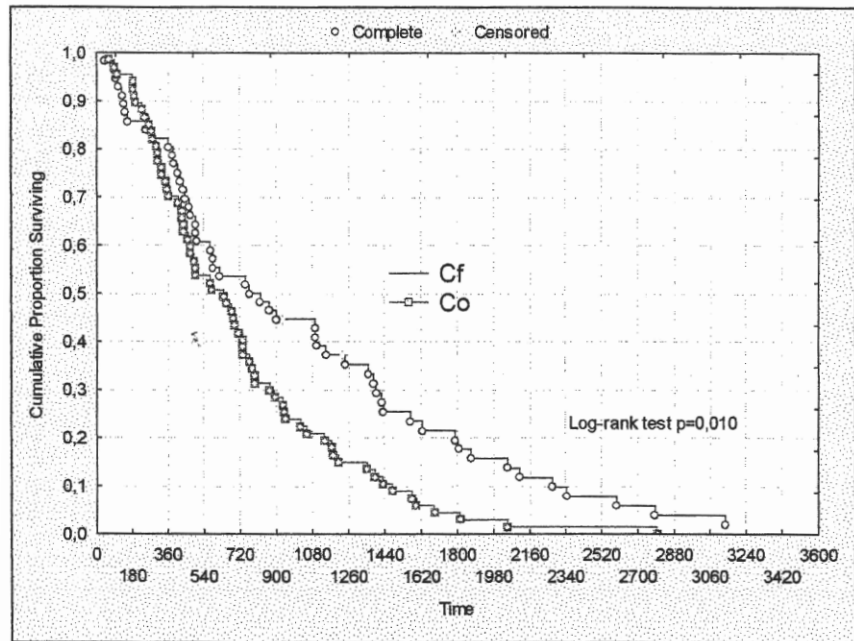


Fig. 1. Overall survival of patients Cf-Co and Co groups (days)

dose of at least 40 Gy.

All patients have been followed from the start of radiotherapy until death or the study closing data (2001). Only acute reactions (RTOG Grade 2–4) and late complications (Grade 2–4) in the rectum and adjacent tissues could be scored.

The calculation of probabilities of survival and comparison of survival curves, the statistical analysis system (SAS) or SPSS, survival analysis, life table method and log-rank, Wilcoxon, chi-square tests were used.

RESULTS

All patients from the Co-Cf group received combined radiotherapy without long interruptions associated with severe acute pelvic morbidity; some patients had a planned gap of 2–3 weeks. Slight acute reactions related with rectal discomfort, increased frequency or change in the quality of bowel habits or frequency of urination usually were observed after a 3.6–4.4 Gy neutron brachytherapy dose. Application of dimethylsulfoxide, meathyluracil and hormone enema was very effective to avoid progression of symptoms.

One month after completion of radiotherapy, local tumour response was estimated among patients in the Co-Cf group: complete response (CR) was achieved in 10 pts (17.9%), partial response (PR) in 30 pts (53.6%), no response (NR) in 11 pts (19.6%) and 5 pts were not qualified.

The 1-, 2-, 3-, 4-, 5-, 6-year survival was 80.4%, 53.6%, 42.7%, 25.6%, 17.7%, 11.8% and 71.6%, 41.8%, 20.9%, 10.5%, 3.0%, 1.5% for the Co-Cf and Co groups, respectively (Fig. 1). The log-rank test showed a significant difference in survival bet-

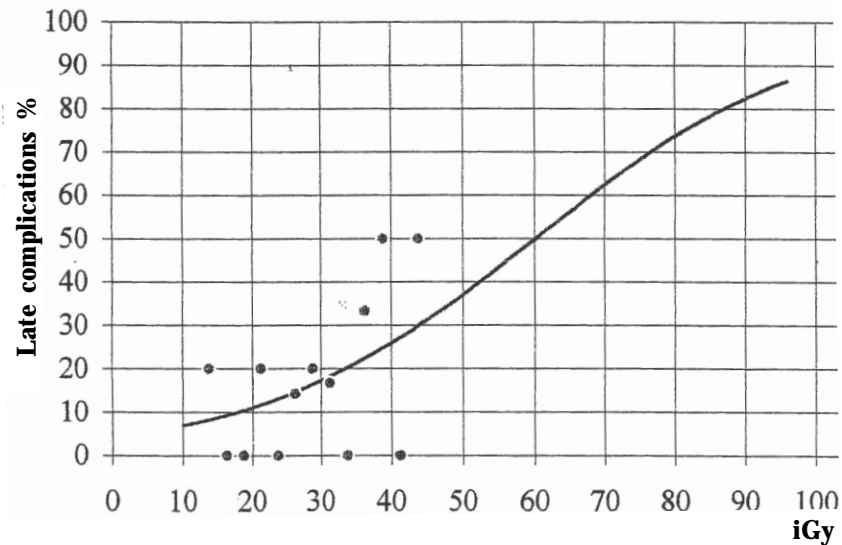


Fig. 2. Probability rate of late complications for Cf-Co group dependent on californium brachytherapy dose (in iGy) plus 37.2 Gy dose from photon external beam radiation therapy

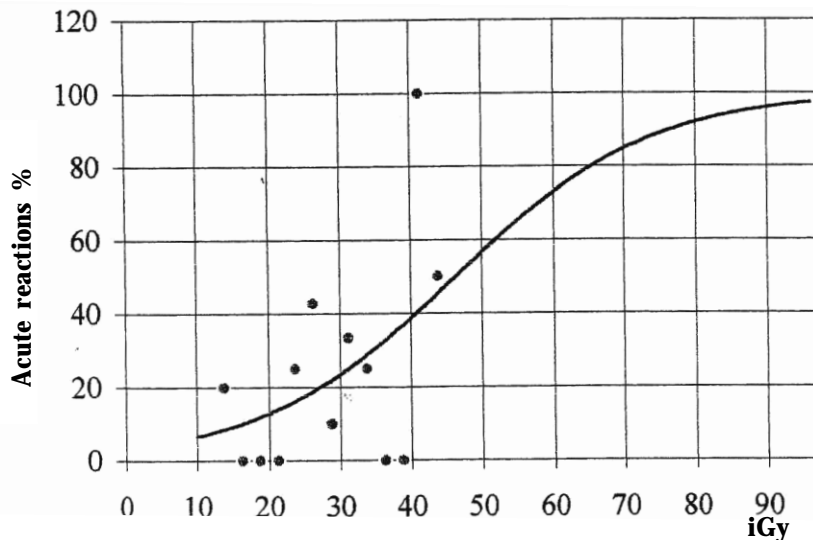


Fig. 3. Probability rate of acute complication for Cf-Co group dependent on californium brachytherapy dose (in iGy) plus 37.2 Gy dose from photon external beam radiation therapy

between the two groups ($p = 0.010$). The median survival time was 27.9 months and 20.6 months for Co-Cf and Co groups, respectively.

Acute bowel reactions (Grade 2–4 using the RTOG scoring system) were assessed throughout the trial. They were observed in 12 (21.7%) cases within 3 months after the completion of radiotherapy: acute rectitis in four and acute enterocolitis in eight cases. The mean total ^{252}Cf brachytherapy dose for patients with acute rectitis was 6.6 Gy.

Late complications were assessed as those arising more than 3 months from completion of radiotherapy with Grade 2–4 morbidity in the RTOG scoring system. In 8 cases out of 50 (16.0%), late bowel toxicity was ascertained: chronic rectitis in 5 pts, enterocolitis in 1 pt, rectum stenosis and chronic ulcer –

1 case of each. The rate of late complications according to californium brachytherapy dose (plus 37.2 Gy from EBRT) showed the 46.26 ± 13.73 iGy dose for probability of late complications in 50% of cases (Fig. 2). These late complications were treated by conservative (6 pts) or surgical (2 pts) procedures.

The 50% probability for acute complications in this group was found to be 60.16 ± 19.32 iGy (Fig. 3).

In 30.0% of the cases acute reactions were observed and late complications in 29.0% of patients from the Co group.

DISCUSSION

Acute and late morbidity are the most important dose-limiting factors in the radiotherapy of rectal carcinoma. Quantitative rectum morbidity in most cases was estimated after external fast neutron radiation therapy and it was reported excellent acute gastrointestinal tolerance of external fast neutrons (15 MeV) in patients irradiated for pelvic malignancies, but late bowel morbidity was higher than could be expected. Duncan et al. [5] analysed the results of randomized treatment of 133 patients with bladder cancer by neutron or photon therapy and concluded that late bowel reactions were significantly worse after neutrons: a neutron dose of 15.2 Gy was estimated as a cause for late complication incidence in 50% of the cases.

The RBE values for acute and late recto-sigmoidal toxicity were 3.4 and 3.8, respectively. Many other authors (11) who used external fast neutron irradiation in the pelvic region of experimental animals, ascertained more severe late bowel reactions. These data allow to conclude that late gastrointestinal morbidity is the main dose-limiting factor for external fast neutron therapy.

Our data show that the occurrence of serious acute and late reactions caused by combined external ^{60}Co gamma and intracavitary ^{252}Cf neutron radiation therapy was much less in comparison with external fast neutron treatment and was at the same level as observed in patients who received curative external ^{60}Co photon therapy. These results correspond to the results obtained by Maruyama et al. (12) who observed

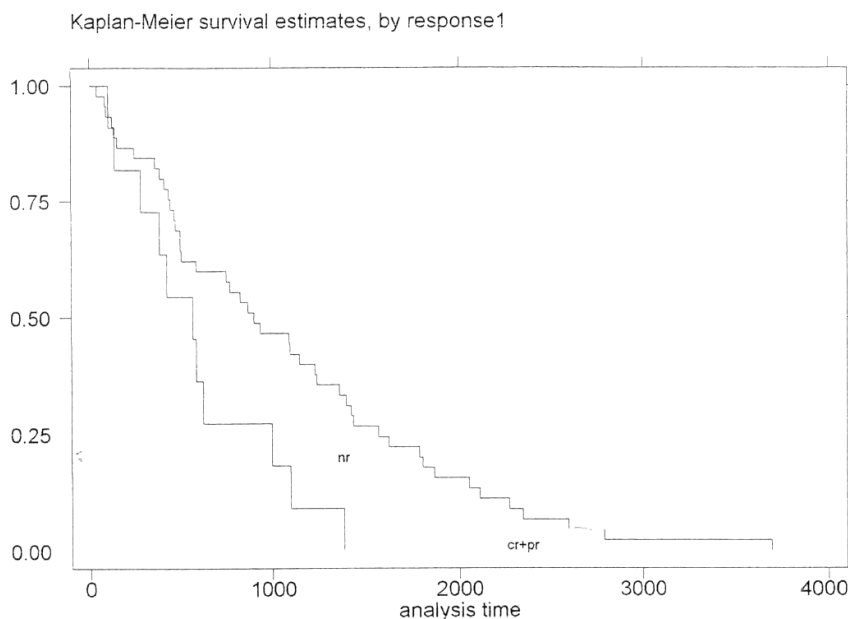


Fig. 4. Overall survival for groups with cr+pr and nr (days)

significantly less complications in the pelvis after curative irradiation of cervix uteri carcinoma with ^{252}Cf brachytherapy. These authors suggested that combining external photon therapy with ^{252}Cf neutron brachytherapy would even lead to a better tolerance in normal tissues and consequently to fewer side-effects and complications. External photon therapy is effective for irradiating large volumes of tissue and can reduce and control minimal or micrometastatic regional diseases. The results support the suggestion that a multimodality type of treatment is one of the best approaches for improvement of cancer treatment. In addition, they confirm the ideas about the advantages of brachytherapy for the results of local treatment.

Local tumour response after radiation therapy might be an important prognostic factor for survival, which depends on the total dose. According to Cox proportional hazard modeling, survival differences between the CR+PR and NR groups should be analysed only for a period of more than 1.5 years, as a significant survival difference between patients with CR+PR and NR starting from a period of 2 years and more (log-rank test $p = 0.0195$; Wilcoxon (Breslow) test $p = 0.0673$) (Fig. 4) was found. The absence of a strong difference during the first 1.5 years might be caused by the small number of patients, short period of survival and difficulties in estimation of local tumour response after a high radiation dose in the rectum. Interestingly, rectal tumour with NR received a neutron brachytherapy dose less than 4 Gy. On the other hand, there were four patients with acute proctitis and a mean neutron brachytherapy dose of 6.6 Gy. These results suggest an optimal ^{252}Cf neutron brachytherapy dose, tolerable for the rectum or adjacent tissues and effective for tumour control.

The survival rate in the Co-Cf group was less than that reported in (5) and higher than in the se-

ries of patients treated with radiotherapy alone at Princess Margaret Hospital with a median survival rate of 14 months and a 5-year survival rate in 5% (13). The survival for the subset of patients with total doses > 50 Gy was comparable (median survival 24 months and 5-year survival 13%) with our results. The other series report similar survival results: 14% at 3 years (14), 31% at 2 years (15).

Although this study was carried out as a non-randomised trial and consequently there was a lot of heterogeneity in tumour characteristics of the patients that included a high proportion of advanced tumours (T3 + T4 83.3%, 8 with recurrences) and older pa-

tients (> 75 yr 44.6%), the results are satisfactory: the survival in the Co-Cf group was significantly (log-rank test $p = 0.010$) better in comparison with the Co group. We therefore agree that the benefit from multidisciplinary approach is only possible if an accurate selection of candidates with "favorable factors" is performed.

On the other hand, Keane and Thomas (16) pointed out that non-experimental clinical data analysis contributes to hypothesis generation and stimulates new ideas which require to be properly tested in the experimental setting of prospective randomised clinical studies.

Analysis of death causes in the Co-Cf group shows that in 58.6% of patients it was tumour progression. One of the explanations for this feature was the low local ^{252}Cf neutron brachytherapy dose (5.18 Gy) compared to a dose of 5.6 Gy in patients who died without tumour progression. The number of deaths from distant metastases is small (8.9%, 5/56) and less than reported by other authors.

Eight patients with rectal recurrences received combined gamma and intracavitary ^{252}Cf neutron radiation therapy, and the survival rate for this group was: 1 years - 88.8%, 2 years - 80%, 3 years - 60%, 4 years - 40%, which was high in this poor prognosis group in comparison with other data (9, 10).

CONCLUSIONS

Combined external ^{60}Co gamma and intracavitary ^{252}Cf neutron radiation therapy was effective in the treatment of locally advanced rectal cancer in comparison to external beam photon radiation therapy alone.

Doses of 37.2 Gy by external gamma irradiation and 5.4 Gy by neutron brachytherapy result in a sa-

tisfactory survival (5 years – 17.7%) and acute (21.4%) or late (16.0%) radiation complication rate.

The achieved results are encouraging and might lead to a further improvement of treatment results for the subset of rectal cancer patients unable to undergo surgery through optimisation of neutron brachytherapy regimens.

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^{252}Cf NEUTRONŲ BRACHITERAPIJA IR IŠORINĖ ^{60}Co FOTONŲ TERAPIJA RADIKALIAI GYDANT PIRMINĄ AR RECIDYVINĄ TIESIOSIOS ŽARNOS VĖPĄ

Santrauka

Šio darbo tikslas – išanalizuoti pacientų, sirgusių pirminiu ar recidyviniu tiesiosios žarnos vėžiu ir gydytų tik suderinta ertmine neutronų ir išorine fotonų spinduline terapija, išgyvenimą, vietinį atsaką ir komplikacijų dažną lyginant su retrospektyvia pacientų grupe, gydyta tik išorine spinduline terapija.

Medžiaga ir metodai. Tiriamąja (Cf-Co) grupė sudarė 56, kontrolinė (Co) – 52 ligoniai. Cf-Co grupės pacientai gavo 37,2 Gy distancinės spindulinės terapijos ir 5,4 Gy ^{252}Cf brachiterapijos dozes, o Co grupės pacientai – vidutiniškai 62,4 Gy. Pacientai stebėti nuo 7,5 iki 12,5 metų.

Rezultatai. Vienerių, trejų ir penkerių metų išgyvenimas sudarė 80,4%; 42,7%; 17,7% bei 71,6%; 20,9%; 3,0% tiriamojame ir kontrolinėje grupėse atitinkamai. Ankstyvos ir vėlyvos komplikacijos stebėtos 21,4% ir 30,0% bei 16,0% ir 29,0% Co-Cf ir Co grupėse atitinkamai.

Išvados. Suderinta neutronų brachiterapijos ir distancinės fotonų terapijos metodika buvo efektyvi gydant vietiniai išplitusią pirminą ar recidyviną tiesiosios žarnos vėžį

Raktažodžiai: tiesiosios žarnos vėžys, neutronų terapija, išorinė fotonų terapija, kalifornis-252